

## **REMARKS**

### **I. Status of the Claims**

Claims 1, 2 and 4-15 are pending in the application, and claims 10-14 stand withdrawn. Thus, claims 1, 2, 4-9 and 15 are under consideration and stand rejected under 35 U.S.C. §103 as obvious. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

### **II. Rejection Under 35 U.S.C. §103**

Claims 1, 2, 4-9 and 15 stand rejected as obvious over either Wreschner A (2005) in view of Hoogenboom *et al.*, Capon *et al.* and Wreschner B (1996). According to the examiner, Wreschner A and Hoogenboom (which are cited as equivalent and shall therefore be addressed together) teach sequences identical to the instant SEQ ID NOS: 19 and 23, but admittedly do not teach chimeras between MUC1 and Fc. These deficiencies are said to be corrected by Capon and Wreschner B, which allegedly teach Fc fusions and various forms of MUC1, respectively. From this, the examiner picks and chooses the relevant teachings from the art to arrive at applicants' invention. Applicants again traverse.

Assuming that the examiner properly characterizes the art with respect to what elements of the presently claimed invention are disclosed in the primary references, Wreschner A and Hoogenboom, the question remains: why would one choose to combine the Fc fusion technology of Capon with the MUC1 teachings of Wreschner A/B and Hoogenboom? The examiner's initial take on this issue was that the skilled artisan would make the combination simply "to prolong the *in vivo* plasma half-life of soluble MUC1 extracellular domains for inhibiting the growth of breast cancer in patients." Yet interestingly, none of the three references

dealing with MUC1, *all of which were published after Capon*, felt any need to cite to Capon, much less incorporate its teachings, to achieve the goal of improved plasma half-life. Thus, it seems that the examiner is in fact substituting her subjective views to what would or would not be obvious to combine, while ignoring fairly clear implications to the contrary from the very people whose art is being cited.

As further evidence that the examiner's thoughts on motivation to combine are wrong, applicants submit the following. Reading Capon, there is no discussion to indicate that adding an Fc molecule to a ligand would have any practical benefit *for producing antibodies*. In fact, it is well accepted that producing antibodies can be achieved, in most cases, simply by repeated administration of significant quantities of antigen. Clearly, as the examiner has shown, MUC1-EC was a well known antigen and could have been produced and administered for the purpose of antibody production without the need to engage in the complicated engineering called for by Capon.

While *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (2007) may have relaxed the standards required for an explicit showing of motivation to combine in the prior art, it nonetheless remains that *KSR* and cases that have followed clearly set forth that motivation to combine remains a vital element of any obviousness rejection. Indeed, as stated in MPEP 2143.01, "A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). "[R]ejections on obviousness cannot be

sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” KSR, 550 U.S. at \_\_\_, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

In response, the examiner argues, in the final Office Action, that “any of a number of ligands can be fused to the Fc region of Capon ....” Precisely! The question, then, is why MUC1-EC? The examiner herself has framed the rejection as one where any of an almost infinite number of antigens might have been selected for combination with the Fc region of Capon. Why would MUC1-EC be a logical choice? Since Capon is silent on this issue, one must turn to the MUC1 references.

Wreschner A discusses, for the most part, the use of *ligands* to MUC1-EC, not MUC1-EC itself. This is reflected throughout the specification, and where it *does* discuss administering MUC1-EC, *it is solely for the purpose of producing antibodies*. As such, the combination of Capon with Wreschner A simply does not make sense. As admitted by the examiner in the final Office Action, there would be no reason to combine MUC1-EC with Fc just to make any antibody.

Wreschner B has a similar, though more subtle inconsistency with Capon. While there *is* a discussion of administering the compositions of Wreschner B to a subject for therapy, the only *claim* directed to that subject matter, claim 14, *carefully excludes subject matter where the MUC1 receptor lacks tandem repeats*. This distinguishing language is also found at page 12 of Wreschner B in the second full paragraph. Thus, while tandem repeat deletions might have been suitable as pharmaceutical agents for the production of antibodies, as in Wreschner A, they were clearly *not* intended for use as therapeutics *per se* in Wreschner B – this is evidenced by the

references own claiming strategy. Again, with the only possible suggested *in vivo* use of such compositions as antibody generating agents, this would *not* precipitate their combination with the complicated Capon technology by one of ordinary skill in the art. It is well established that an examiner cannot pick and choose from a reference only those portions of the reference that comport with the rejection while at the same time disregarding teachings that are wholly inconsistent with the rationale underlying the argument for obviousness. A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Moreover, it is a well known patent law tenet that the properties of a compound must be considered in determining the patentability of that compound. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). In that regard, appellants previously provided the declaration of one of the inventors, Dr. Surender Kharbanda, that contains data showing that an Fc-MUC1-ED fusion has activity against cancer cells both *in vitro* and *in vivo*. While Wreschner (A) suggests administering a MUC1-EC peptide to subjects for the treatment of cancer, the clear implication of that reference is that the peptide will be generating protective antibodies. Nothing in Wreschner (A), or any other cited reference for that matter, suggests that the peptide could *directly* inhibit cancer cells. The examiner's rebuttal is to simply waive off this argument, finding that the reported activity was indeed presaged by the cited references. If this were actually true, why would the art (Wreschner B) have carefully excluded such an embodiment from their claims? There is no reason, and as such, the examiner's unsupported conclusions are incorrect. Thus, this feature of the claimed invention was entirely unpredicted by the cited art.

Applicants now provide a second Rule 132 declaration from Dr. Kharbanda with data only obtained since the filing of the previous response (see “good faith” requirement of MPEP §714.12). First, to assess the effects of GO-101 on sensitivity of human carcinoma cells to oxidative stress, the inventors treated ZR-75-1 breast carcinoma cells with 500 nM GO-101 in the presence and absence of 1.0 mM H<sub>2</sub>O<sub>2</sub>. As a control, cells were also separately treated with hFc (data not shown). Following treatment for 3 days, viable cells were then counted using trypan blue exclusion. The results demonstrate that ZR-75-1 cells exposed to H<sub>2</sub>O<sub>2</sub> exhibited ~66% inhibition in cell proliferation compared to mock conditions. Importantly, the ZR-75-1 cells exposed to 500 nM GO-101, but not hFc, was associated with ~42 % growth inhibition. However, there was a ~90% growth inhibition when cells were treated with both H<sub>2</sub>O<sub>2</sub> and GO-101 (Fig. 2).

Next, ZR-75-1 human breast carcinoma cell were treated with various concentrations of GO-101 starting from 2  $\mu$ M with 2-fold serial dilutions to obtain a total of 8 different concentrations in the presence or absence of doxorubicin starting from 25 nM with 2-fold serial dilutions to obtain a total of 8 different concentrations. Cells were also separately treated with multiple concentrations of doxorubicin starting from 25 nM with 2-fold serial dilutions to obtain a total of 8 different concentrations. Cells in duplicate wells were treated with either alone (doxorubicin or GO-101) or in combinations for 4 days. On day 5, the medium in the plate was replaced with 10% alamarBlue solution and incubated for various time points (1-5 hrs). At the end of each hour, absorbance of the plate was measured at 570 nm and 600 nm as reference. A set of blank wells were maintained with medium alone and medium with alamarBlue for the purpose of calculating actual absorbance. Obtained absorbance values were plotted against respective concentrations of GO-101, doxorubicin or in combination of GO-101 and doxorubicin

The results demonstrate that there was a very little inhibition of cell proliferation at low doses of either agent alone. However, there is a substantial reduction in cell proliferation when the two agents combined. Fig. 3 indicates a representative plot obtained for one of the assays performed with these conditions.

Finally, nude mice were treated with doxorubicin at 6 mg/kg given every fourth day for three injections, plus GO-101 (1 mg/kg, daily x 21). The treatment was apparently tolerated, producing no “treatment-related” toxicity. Treatment with doxorubicin produced significant ( $p = 0.0356$ ) anti-tumor activity based upon tumor growth delay. Doxorubicin treatment produced neither tumor regressions nor tumor free survivors. Combination treatment with doxorubicin + GO-101 produced a significant inhibition of tumor growth to that compared with Doxorubicin alone (Fig. 4). Two out of 5 animals in this group had complete tumor regressions. Although this treatment regimen appeared to produce more tumor regressions compared to single agent therapy, suggesting enhanced anti-cancer activity.

To conclude, applicants submit that the examiner, while correctly identifying many of the elements of the claimed invention in the cited art, has abandoned entirely the requisite element of motivation to combine. It simply is *not* enough that the references might be *combinable* – the results also need to have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) (“If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.”). Looking at the art cited here, as well as the evidence of *in vitro* and *in vivo* activity of the claimed compositions, there is no reasonable belief (a) that the

references would have been combined as posited, or if they had (b) if they had, (b) that they could have in any way predicted the ability of the claimed compositions to be therapeutically active in their own right, as opposed to being employed as immunogens. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

### **III. Conclusion**

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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